33 Paragangliomas: A Case Series from Burdenko Center of Neurosurgery

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33.1 Introduction

The incidence of paragangliomas (PGLs) has been reported as 1 in 1.5 million people per year [1–3]. Women are affected more frequently than men, with reported ratios of 6:1 to 6:4 [4]. PGL is classified by the WHO as a tumor of indeterminate biology M code XXXX1 [5]. Malignant paragangliomas are uncommon, and their diagnosis can only be confirmed by the presence of metastatic disease. Although all mutated SDHx genes carry a risk for metastasis, SDHB mutations confer the highest risk at ~30%, SDHD carriers have smaller risk of about 3–4%. SDHB mutations are also associated with the poorest survival (11–36% at 5 years) [6]. Multicentric tumors occur in 10–20% of all head and neck paragangliomas [7]. However, reports of much higher incidence of multiple tumors, like 40% for sporadic form and 80% for familial variety, can be found in the literature [8].

In the head and neck region, the most common location of PGL is at the carotid body (60%), followed by the temporal bone (glomus tympanicum, 18%), arising from paraganglia associated with Arnold and Jacobson nerves within the middle ear, or glomus jugulare (12%), arising from paraganglia in the adventitia of the jugular vein, and upper pharyngeal space (glomus vagale, 5%), arising from the inferior vagal ganglion [9]. The most effective treatment modality for PGLs remains undetermined. Their involvement of major vessels, proximity to cranial nerves, and their propensity for intracranial extension can result in significant morbidity from surgical resection. Complications from resection include stroke (8–20%), cranial nerve injury (7–49%) [10], meningitis (6–9%), and cerebrospinal fluid leak (8.3%). In addition, the overall mortality rate was 1–5% [11]. Radiation therapy has the advantage of avoiding the morbidity of surgery while offering an equal possibility of cure. Among the 804 patients included in 34 different radiotherapy series between 1962 and 2009, the median local control rate is generally in excess of 90% [12]. Patients achieved symptomatic improvement in more than 70% of cases across 34 published series [13], and partial/complete resolution of symptoms can be estimated to be achieved in more than 60% of cases [14, 15].

33.2 Rationale for Radiation Therapy

The first review of the literature concerning the place of radiotherapy in the management of the head and neck paragangliomas was made by

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Springate and Weichselbaum [16]. Nineteen series reporting 379 patients treated between 1932 and 1983 were reviewed. These patients received radiotherapy as the primary, preoperative, postoperative, or salvage treatment. Of 405 patients treated by surgery, 349 (86%) were reported as locally controlled. Of 379 patients who received radiotherapy, 344 (90%) were locally controlled, whereas the control rate for radiotherapy without surgery was even higher: 182 of 195 (93%) patients. Despite high control rates, external beam radiation requires large field sizes, resulting in high rate of complications: radionecrosis of the bone, brain necrosis/abscess, and xerostomia [17]. The advent of intensity-modulated radiation therapy has reduced the extent of normal tissue exposed to radiation, which in the future will likely be accompanied by a decrease in side effects.

With the development of technology, intensity-modulated radiotherapy (IMRT) delivers a highly conformal, three-dimensional (3D) distribution of radiation doses that is not possible with conventional methods. Henzel et al. [18] reported no severe (grade 3 or 4) acute or late toxicity in 16 patients, and 100% freedom from progression, with a median dose of 57 Gy. Mendenhall W.M. et al. [19] summarized the long-term outcomes of 149 patients treated with RT between May 1968 and September 2016 at the University of Florida College of Medicine. IMRT has been used to treat essentially all patients since 2001. No patient developed a new CN palsy after RT. No patient experienced a severe complication after RT or developed a radiation-induced malignancy. Table 33.1 shows the main series on conventionally fractionated radiotherapy treatment of PGLs.

33.3 Single-Fraction Radiosurgery

Compared with conventional radiotherapy, stereotactic radiosurgery involves a shorter treatment time (it usually takes 1 day, compared with 4–6 weeks for conventionally fractionated external beam radiation and with several weeks of postoperative recovery for resection), precise stereotactic localization, and a small volume of irradiated normal tissue. In 1997, Foote et al. [20] published the first report as a preliminary study. The goal of their study was to evaluate the immediate, acute, and chronic toxicity and the efficacy of stereotactic radiosurgery in patients with unresectable or subtotally resected glomus tumors. No acute or chronic toxicity was demonstrated, and eight of nine tumors remained stable in size at a median clinical follow-up duration of 20 months.

Recently, Shapiro et al. carried out very interesting meta-analyses on tumor control, symptomatic control, and complication rates of stereotactic radiosurgery as the primary treatment of glomus jugulare tumors [21]. The inclusion criteria were (1) no previous treatment of any kind, (2) follow-up with magnetic resonance imaging for at least 12 months, and (3) reported pre- and post-treatment symptoms, tumor control, or complications. Fifteen studies on 91 patients met the criteria. Tumor control was achieved in 92% of patients, symptoms control - in 93%, and complications occurred in 8%. There was one major complication. The recommended marginal tumor dose (prescribed most commonly to the 50% isodose line when the Gamma Knife is used) is 15–18 Gy, resulting in a maximum dose of 30–36 Gy. Table 33.2 shows the main series on single-fraction SRS treatment of PGLs.

33.4 Hypofractionated Radiotherapy

The efficacy and feasibility of CyberKnife radiotherapy was initially reported by investigators at Stanford University where patients were treated to a dose of 14–25 Gy in a single fraction or 18–25 Gy in three fractions [22, 23]. An Italian series of nine patients treated with CyberKnife radiotherapy for skull base paragangliomas reported doses ranging from 11 to 13 Gy in a single fraction and 24 Gy in three fractions [24]. In this series, local control was 100%, and 25% of patients had improvement in their symptoms. The results of these clinical series suggest that

Table 33.1 Summary of clinical series of conventionally fractionated radiotherapy for treatment of head and neck paragangliomas

Author	Place	Year	Treatment modality	No. of patients	Follow-up (years)	Tumor control	Toxicity
Nguyen [27]	Grenoble, France	1973–1996	EBRT	18	5.5	75% (5 years)	Radionecrosis
Lightowlers [28]	Cambridge, Great Britain	1998–2008	EBRT/IMRT	21	4.5	95% (5 years)	Xerostomia
Chino [29]	Durham, NC, USA	1963–2005	EBRT	31	9	96% (5 years) 90% (10 years)	Xerostomia, cataract
de Jong [30]	Houston, TX, USA	1956–1991	EBRT	38	11.5	79% primary RT, 100% combined treatment, 91% salvage RT	?
Combs [31]	Heidelberg, Germany		SRS/SRT/IMRT	39	10.5	97% (10 years)	Maxillary bone abscess, middle ear effusion
Breen [32]	Rochester, MN, USA	1973–2015	EBRT/IMRT	41 with malignant PG	9.7	81% (5 years)	Neuropathy
Huy [33]	Paris, France	1988–2003	EBRT	41	5.5	96%	Xerostomia, serous otitis media
Pemberton [34]	Manchester, UK	1965–1987	EBRT	49	7.4	92% (5 years) 92% (10 years)	None
Powell [35]	Boston, MA, USA	1949–1985	EBRT	64	9	73% (25 years) 100% combined treatment	Facial nerve palsy
Dupin [25]	Paris, France	1990–2009	EBRT	66	4.1	100% (5 years) 98.7% (10 years)	Xerostomia, stroke, radionecrosis, aphthous ulcer
Mendenhall [19]	Gainesville, FL, USA	1968–2016	SRS/SRT/EBRT	149	11.1	99% (5 years) 96% (10 years)	None
Total				557		93.6 (5 years) 95.6 (10 years)	

Table 33.2 Summary of clinical series of stereotactic radiosurgery for treatment of head and neck paragangliomas

Author	Place	Year	Treatment modality	No. of Patients	Follow-up (months)	Tumor response				CN morbidity (pts)
						Regression	Stable	Progression	Unknown	
Hurmuz [36]	Ankara, Turkey	2007–2010	CK	14	39 (7–60)	6	8	0	0	0
Schuster [37]	Nashville, Tennessee, USA	1998–2014	LINAC	14	31.7 (18.6–56.1)	6	7	1	0	1 (7%)
de Andrade [38]	São Paulo (SP), Brazil	2006–2011	LINAC	15	35.4 (3–61)	0	15	0	0	0
Bitaraf [39]	Tehran, Iran	2004–2006	GK	16	18.5 (4–28)	6	8	0	2	1 (6%)
Genç [40]	Istanbul, Turkey	1999–2008	GK	18	52.7 (12–116)	17	0	1	0	1 (5.5%)
Gerosa [41]	Verona, Italy	1996–2005	GK	20	51 (12–110)	9	11	0	0	1 (5%)
Marchetti [42]	Milan, Italy	2004–2014	CK	20/21	46.3 (12–111)	7	11	0	3	3 (15%)
El Majdoub [43]	Cologne, Germany	1991–2011	LINAC	27	9.6 years (5–19)	12	15	0	0	1 (3.7%)
Sallabanda [44]	Madrid, Spain	1993–2014	29 LINAC, 2 CK	30/31	4.6 years (1.5–12)	9	21	1	0	1 (3%)
Lieberson [13]	Stanford, CA, USA	1991–2009	6 LINAC, 30 CK	36/41	3.9 years (0.32–15.45)	18	19	0	4	4 (11%)
Winford [45]	Winston-Salem, NC, USA	2000–2015	GK	38	39.1 (5.5–141)	29		4	5	10 (26%)
Martín [46]	Granada, Spain	1997–2012	LINAC	39	71 (3–200)	22	14	3	0	7 (17.9%)
Hafez [47]	Cairo, Egypt	2005–2014	GK	40	84 (36–156)	12	27	1	0	3 (7.5%)
Sharma [48]	Cleveland, OH, USA	1997–2016	GK	42/43	62.3 (3–219)	31	1	6	5	8 (19%)
Liscak [49]	Prague, Czech Republic	1992–2003	GK	46	118 (12–217)	34	9	1	2	2 (4%)
Ibrahim [50]	Newport, United Kingdom	1994–2010	GK	75/76	51.5 (12–230)	43	28	5	0	12 (16%)
Patel [51]	Rochester, MN, USA	1990–2017	GK	85	66 (7–202)	41	14[a]	5	25	2 (3%) 7 NSH (20%)
Sheehan [52]	8 USA GK centers	1988–2010	GK	132/134	50.5 (5–220)	49	65	0	20	15 (11%)
Total				707						4 (0.6%)

[a]Tumor growth <15%; *NSH* Non-serviceable hearing

Table 33.3 Summary of clinical series of conventionally hypofractionated stereotactic radiotherapy for treatment of head and neck paragangliomas

Author	Place	Year	Fractions # × doses (Gy)	No. of patients	Follow-up (months)	Tumor control	CN morbidity (pts)
Lim [53]	Stanford, CA, USA	1991–2006	3 × 6–8.5	6	60 (6–162)	100%	3
Tosun [54]	Istanbul, Turkey	2009–2014	3 × 7–10 5 × 5	12	30 (0–66)	100%	0
Tse [55]	San Francisco, CA, USA	2010–2012	3 × 7–8 5 × 5–6	12	52 (31–74)	92.3%	8
Hurmuz [36]	Ankara, Turkey	2007–2010	5 × 5–6	13	39 (7–60)	100%	0
Lieberson [13]	Stanford, CA, USA	1991–2009	2 × 9–10 3 × 6.5–8 5 × 5	14	3.9 years (0.32–15.45)	100%	4
Marchetti [42]	Milan, Italy	2004–2014	3 × 8 5 × 5–6	14	46.3 (12–111)	100%	3
Chun [56]	Dallas, TX, USA	2007–2013	5 × 5	31	24 (4–78)	100%	2
Total		1991–2014		102		98.9%	3

CyberKnife may be used to treat PGLs with hypofractionated stereotactic radiotherapy that results in equivalent treatment outcomes as conventionally fractionated radiotherapy with improved patient convenience.

The experience of CyberKnife radiotherapy for treatment of the head and neck paragangliomas gained to date is presented in Table 33.3. The most frequently used regimens are three fractions per 8 Gy and five fractions per 5–6 Gy.

33.5 Toxicity

33.5.1 Acute Toxicity

Acute toxicity (during RT and within 3 months of its completion) can present with nausea, dermatitis with severe desquamation and fragility of the external auditory canal skin, headache, xerostomia, weight loss, mucositis, or ophthalmic zoster. After radiation treatment of PGLs, adverse events are rare and usually mild or moderate (grades 1–2). Only in a study Dupin et al. [25] described grade 3–4 acute toxicity: 9 out of 66 patients were hospitalized for weight loss, nausea, grade 3 mucositis, or ophthalmic zoster.

33.5.2 Late Toxicity

Springate and Weichselbaum [16] in the first systematic literature review of treatment modalities for paragangliomas of the temporal bone showed that complications after radiotherapy are very rare: bone necrosis (1.7%), brain necrosis/abscess (0.84%), and second malignant transformation (fibrosarcoma, 1 of 356 or 0.28%). These severe complications were observed in the dose range of 54–70 Gy. Complications became less frequent and less pronounced with the introduction of stereotactic RT and SRS.

33.6 Cranial Nerve Morbidity

Following SRS of jugular paragangliomas, 9.7% of patients had a post-treatment cranial nerve (CN) IX deficit, 9.7% had a post-treatment deficit of CN X, 12% had a post-treatment deficit of CN XI, and 8.7% of patients had a post-treatment CN

XII deficit. Importantly, patients suffered from lower cranial nerve neuropathy when treated with SRS alone [10]. Patients undergoing gross total resection reported worse rates of CN IX–XI deficit compared to those undergoing SRS. However, the CN XII deficit rates were comparable.

The auditory results after stereotactic radiosurgery for jugular paraganglioma are only described in detail in a study by Patel et al. [26] at the Mayo Clinic (Rochester, MN, USA): 7 out of 35 patients developed non-serviceable hearing. The estimated hearing preservation rates according to Kaplan-Meier at 1, 3, and 5 years after SRS were 91%, 80%, and 80%, respectively.

33.7 Own Experience

Three hundred and sixty-six patients with 381 PGLs were treated with SRS and SRT at our center between March 2005 and December 2018. From April 2009 to December 2018, 158 patients with 162 paragangliomas (127 women and 31 men) were treated with CyberKnife G4 system. The median age was 52 years (range 12–84). Forty-four patients have undergone microsurgery (28%), 12 of them repeatedly, 3 patients were operated 3 times, and 1 was operated 9 times. Eleven of the patients (7%) had undergone embolization alone before irradiation. CyberKnife radiosurgery was the primary treatment modality in the remaining 103 patients (65%). When surgery was not performed and thus the histological diagnosis was not confirmed, the diagnosis was based on CT and CT perfusion, MR imaging, angiography, and clinical findings. There were 85 jugulotympanic paragangliomas, 35 tumors of the glomus jugulare, 23 of glomus tympanicum, 8 carotid body paragangliomas, 5 tumors of the glomus vagale, 1 paraganglioma of the glomus ciliare, 1 spinal paraganglioma of the filum terminale, and 4 metastases of malignant paragangliomas.

Twenty-three paragangliomas with a mean of volume 3 cm^3 (range 0.5–7.7) were irradiated using a single fraction. Mean radiosurgical dose was 17.5 Gy (range 15–24). The higher mean doses of 22 and 24 Gy were used for metastasis of malignant paragangliomas. One hundred thirty-nine lesions with mean volume 17.6 cm^3 (range 0.2–73) underwent multisession CK treatment with the following regimes: 3 fractions per 7 Gy (74 cases–53%), 5 fractions per 5.5–6 Gy (54 cases–39%), and 7 fractions per 4.5–5 Gy (11 tumors—8%).

The median follow-up was 36 months (range 5–105). Follow-up time was calculated from the last day of the CK procedure. Seventeen patients were lost to follow-up. Forty-six percent of the patients had noticeable tumor shrinkage. In 72 patients (50%), the tumor size remained unchanged.

According to MRI control, the progression of tumor growth was observed in six cases (4%) after treatment: two of them were metastases of malignant paragangliomas (there were CK re-radiation treatments that were used after the conventional fractionation of RT). In two cases with follow-up less than 1 year, minimal tumor enlargement was observed. In these cases, verification of the real continuous growth was required, and we continue to monitor these patients. As a result, actuarial local control was 96% at 3 years.

33.8 Clinical Case

A 45-year-old female patient was to the center to pulsatile tinnitus and reduced right-side hearing, which had occurred over the previous 7 years. The patient was also experiencing dizziness with nausea and vomiting, which occurred occasionally. Partial surgical excision with previous endovascular embolization was performed via a trans-canal approach 7 months before irradiation. After surgery and embolization, the patient had VII, IX, X, and XII CN dysfunction. Control MRI (Fig. 33.1a) showed a jugulotympanic paraganglioma with a pronounced extracranial extension (tumor volume was 17.8 cm^3). We treated her with hypofractionated radiotherapy with the CyberKnife (Fig. 33.1b) with a mean dose of 30 Gy in five fractions (prescribed dose 27 Gy to the 79% isodose line). A marked shrinkage of the tumor was noted on MR images at 4 years after SRT (Fig. 33.1c). There was no acute or chronic toxicity after procedure. The patient had improvement of IX and X cranial nerves function after CK treatment.

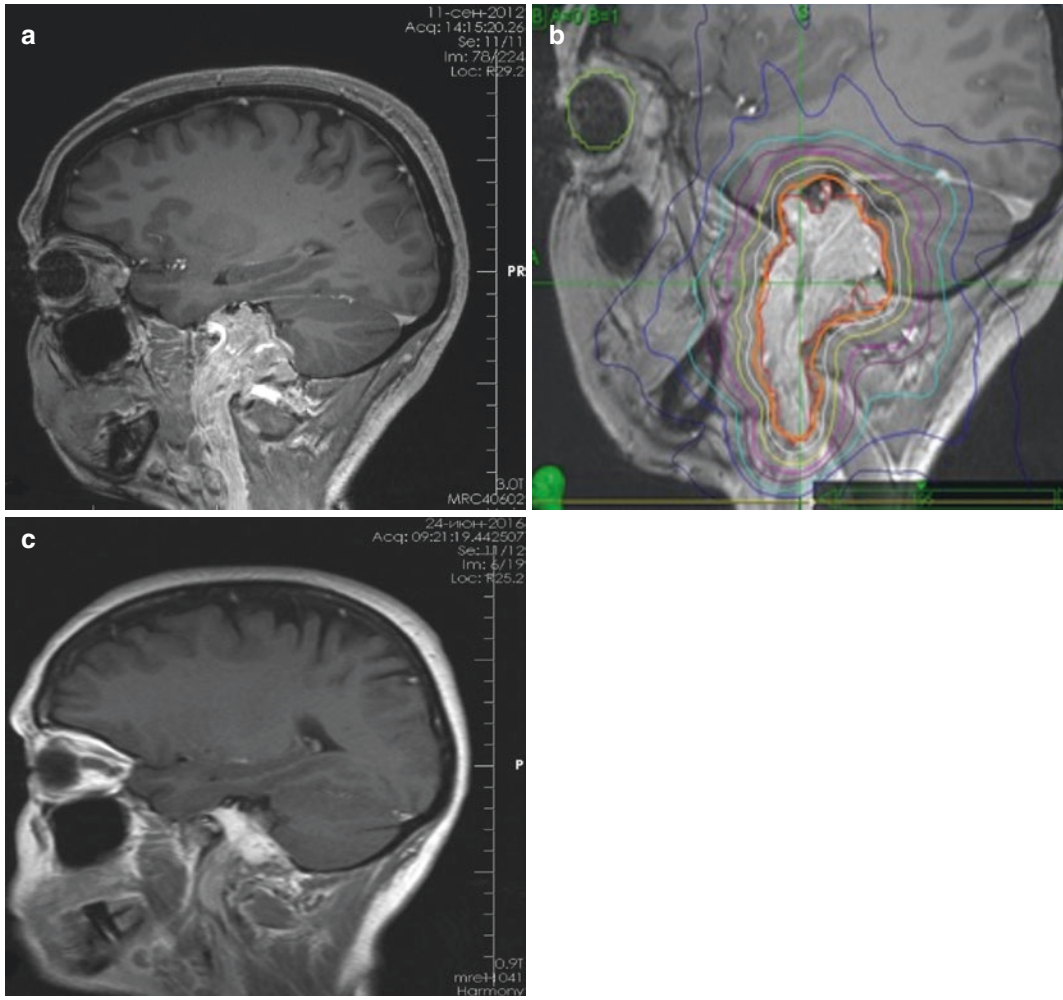

Fig. 33.1 (**a**) Pre-treatment MRI of a jugulotympanic paragangliomas with a pronounced extracranial extension (tumor volume was 17.8 cm^3). (**b**) CyberKnife treatment plan (five fractions per 6 Gy). Prescribed dose was 27 Gy to the 79% isodose line. (**c**) Post-treatment MRI obtained 4 years after SRT showing a marked shrinkage of the tumor

33.9 Conclusion

We have presented a brief history and overview of radiation treatment for glomus jugulare tumors, focusing on recent radiosurgical results. Due to the complex anatomy surrounding the tumors, resection often carries high rates of morbidity and mortality. Since 2000, multiple GKS-, LINAC-, and CyberKnife-based series have been reported. Collectively, they show excellent tumor control and relatively low complication rates. Table 33.4 summarizes practical suggestions for hypofractionated treatment of head and neck paragangliomas. Although longer-term follow-up studies are still in progress, the results in outcome studies published to date as well as our own data are good enough to justify the use of stereotactic irradiation as a method of choice and first-line treatment strategy for glomus jugulare tumors. The main problem in cases without histological conformation is differential diagnosis of paragangliomas with other tumors as benign (schwannomas, meningiomas, capillary hemangiomas, etc.) and malignant tumors (cancers, sarcomas, endolymphatic sac tumors, etc.) of the temporal bone and neck.

Table 33.4 Practical guide for hypofractionated treatment of head and neck paragangliomas

Parameter	Suggestion
Imaging	CT or MRI perfusion for differential diagnosis 3D T1 $_{TCE}$ MPRAGE, VIBE, or SPGR 3D T1w/o CE MPRAGE, VIBE, or SPGR Volumetric T2
Maximal tumor volume	75 cm^3 (may be less with substantial intracranial extension and brain stem compression)
Number of fractions	3 5
Mean dose per fraction (Gy)	7.5 6
Dose to the brain stem	<18 Gy for 0.15 ccm for 3 fractions <22.5 Gy for 0.15 ccm for 5 fractions
Dose to the cochlea	<15 Gy for 5% for 3 fractions <22 Gy for 5% for 5 fractions
10-year expected tumor control	95%
Serviceable hearing preservation at 5 years	>80%
Malignant transformation	<0.28%

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